JOC Article

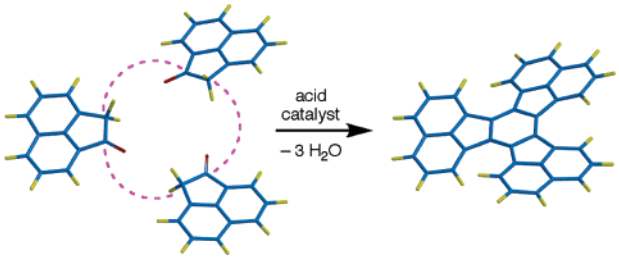
# Trisannulated Benzene Derivatives by Acid Catalyzed Aldol Cyclotrimerizations of Cyclic Ketones. Methodology Development and Mechanistic Insight

Aaron W. Amick and Lawrence T. Scott*

*Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467-3860*

*lawrence.scott@bc.edu*

*Received January 13, 2007*




Several factors that contribute to the success of aldol cyclotrimerizations have been clarified as part of an effort to shed light on the inner workings of this century old reaction. The use of 4,7-di-*tert*-butylacenaphthenone (**11**) as a mechanistic probe molecule has led to intriguing discoveries about temperature, solvent, and solubility effects. Solvents that are both polarizable and somewhat polar, e.g., *o*-dichlorobenzene (ODCB), work best for the aromatic ketones examined. Certain Brønsted acids were found to work better than Lewis acids as catalysts for the archetypal aldol cyclotrimerization of indanone (**2**) in aprotic solvents, and a strong dependence on the p$K_a$ of the acid was observed. A standardized protocol, using *p*-toluenesulfonic acid monohydrate, is shown to work well in a number of test cases.

## Introduction

For the construction of triply annulated benzene rings that have $C_3$ or $C_{3h}$ symmetry, nothing rivals the one-pot, acid-catalyzed, head-to-tail cyclotrimerization of cyclic ketones—when it works.[1,2] The heptacyclic $C_{27}H_{18}$ hydrocarbon truxene (**1**), for example, can be prepared in 85% isolated yield simply by refluxing indanone (**2**) in a 1:2 mixture of concentrated HCl and acetic acid.[1b,3] Scheme 1 outlines the presumed overall mechanistic pathway for this remarkable transformation. The stereochemistries of the "dimer" and "trimer" are of little concern, because rotational barriers in the "trienol" are not expected to be large, at least in the case illustrated.

Though first discovered in the 1800s,[4] this reaction has enjoyed scant popularity as a synthetic tool, largely on account of its unpredictability. Many cases give low yields or fail completely.[1] Under conditions that work well with indanone, for example, the closely related aromatic ketone α-tetralone (**3**) yields no more than traces of the expected cyclotrimerization product (**4**), and acenaphthenone (**5**) gives less than 5% yield of decacyclene (**6**).[5]

In this paper, we provide insights into some of the factors that can scuttle such cyclotrimerizations and offer recommendations on how to choose solvents, temperatures, acid catalysts, etc. that will circumvent some of the pitfalls. Certain ketones,

(1) (a) For a review of early work on the aldol cyclotrimerization reaction, see: Boorum, M. M.; Scott, L. T. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley: New York, 2002; Chapter 1. (b) De Frutos, O.; Gomez-Lor, B.; Granier, T.; Monge, M. A.; Gutierrez-Puebla, E.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 204−207. (c) Boorum, M. M. Ph.D. dissertation, Boston College, 2001. (d) Zhang, W.; Cao, X.-Y.; Hong, Z.; Pei, J. *Org. Lett.* **2005**, *7*, 959. (e) Aly, A. A. *Tetrahedron Lett.* **2005**, *46*, 443. (f) Terai, H.; Takaya, H.; Naota, T. *Tetrahedron Lett.* **2006**, *47*, 1705. (g) Yuan, M.-S.; Fang, Q.; Liu, Z.-Q.; Guo, J.-P.; Chen, H.-Y.; Yu, W.-T.; Xue, G.; Liu, D.-S. *J. Org. Chem.* **2006**, *71*, 7858.

(2) For more lengthy stepwise alternatives, see: (a) Hagen, S.; Scott, L. T. *J. Org. Chem.* **1996**, *61*, 7198−7199. (b) Mehta, G.; Srirama Sarma, P. V. V. *Tetrahedron Lett.* **2002**, *43*, 9343−9346 and references cited therein.

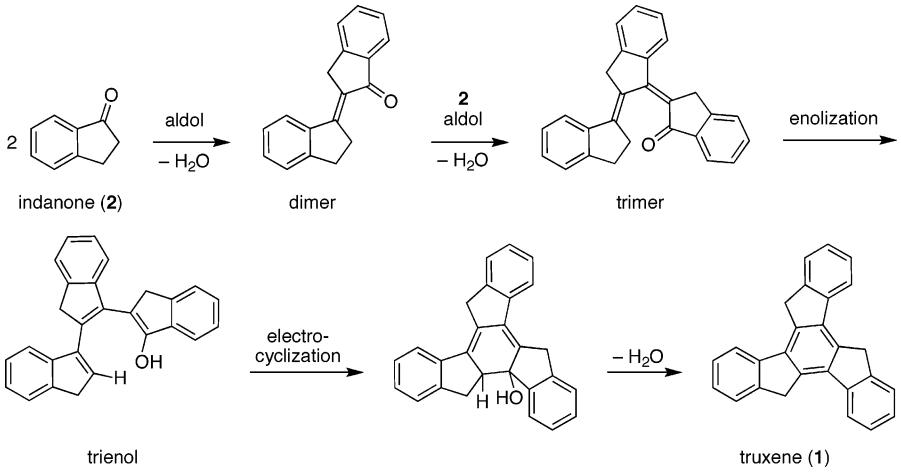
(3) Dehmlow, E. V.; Kelle, T. *Synth. Commun.* **1997**, *27*, 2021−2026. Note: De Frutos et al. report an 85% yield for purified truxene,[1b] whereas the 98% yield reported by Dehmlow et al. is based on the weight of unpurified precipitate from the reaction.

(4) (a) Wislicenus, W. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 589−595. (b) Hausmann, J. *Ber. Dtsch. Chem. Ges.* **1889**, *22*, 2019−2026. (c) Kipping, F. S. *J. Chem. Soc.* **1894**, *65*, 269−289. (d) Kipping, F. S. *J. Chem. Soc.* **1894**, *65*, 480−503.

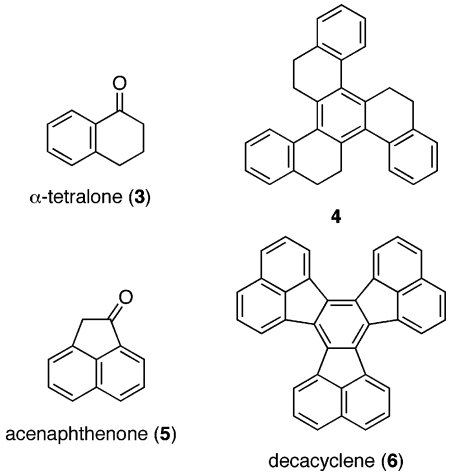
(5) Not previously published; see the Supporting Information.

10.1021/jo070080q CCC: $37.00 
Published on Web 03/24/2007

**SCHEME 1**



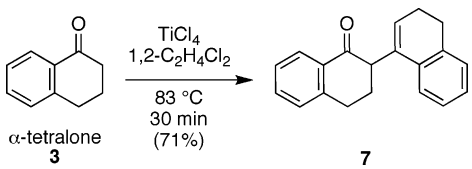

such as α-tetralone (**3**), are doomed from the start, for reasons discussed below, whereas useful conditions can be found for others, such as acenaphthenone (**5**). These and related case studies are presented herein. Hopefully, our results will prove helpful to others who seek to exploit this powerful reaction. We note at the outset, however, that *many questions remain unanswered*.




## Results and Discussion

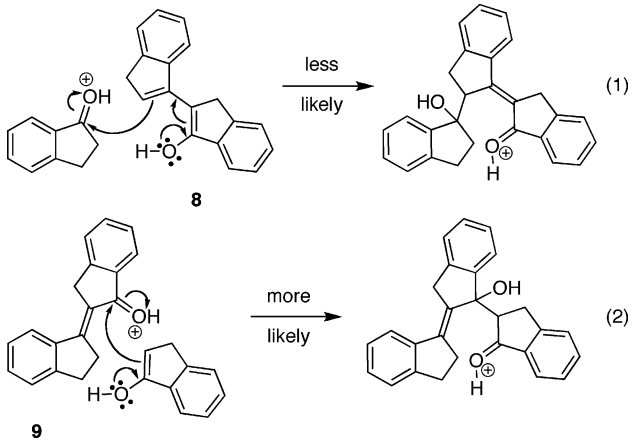
**First Requirement: Dimer Must be α,β-Unsaturated**. Dehydration of the initial aldol product to produce a β,γ-unsaturated dimer as the thermodynamically preferred enone spells death for the aldol cyclotrimerization.[1] The failure of α-tetralone (**3**) to give a cyclic trimer (**4**) can be traced to precisely this problem. Under all conditions we have examined, the acid-catalyzed aldol condensation of α-tetralone (**3**) produces the β,γ-unsaturated dimer (**7**) and stops there (e.g., Scheme 2).[2a] Density functional theory confirms that both geometric isomers of the α,β-unsaturated dimer lie higher in energy than **7** in this case.[1]

**SCHEME 2**




In the α-tetralone example (Scheme 2), dimer **7** builds up in concentration until all of the starting material has dimerized. At that point, the dimer finds no monomer left with which to condense, and the reaction stops.[6] One is forced to conclude that, in this case, the second aldol step (dimer + monomer → trimer) must be significantly *slower* than the first one (monomer + monomer → dimer). By contrast, in the indanone example (Scheme 1), the second aldol step must be significantly *faster* than the first, because virtually no dimer is left stranded when the last molecules of monomer disappear.

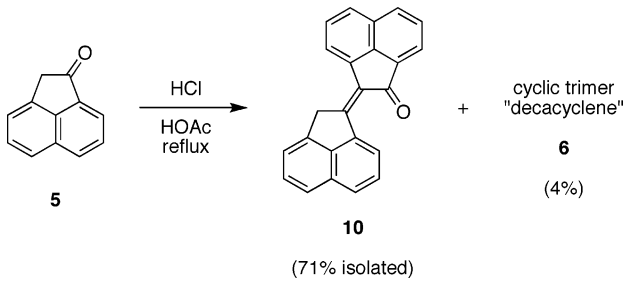
Why should the position of the double bond affect the rate of the second aldol condensation step? The answer lies in the details of the second reaction (dimer + monomer → trimer). The C−C bond-forming step for this aldol condensation involves nucleophilic attack by the enol of one partner on the protonated carbonyl group of the other. In principle, that coupling could be accomplished in either of two ways, as illustrated in eqs 1 and 2 for indanone. Protons are used in these equations as generic representations for the acid catalyst (discussed further below).



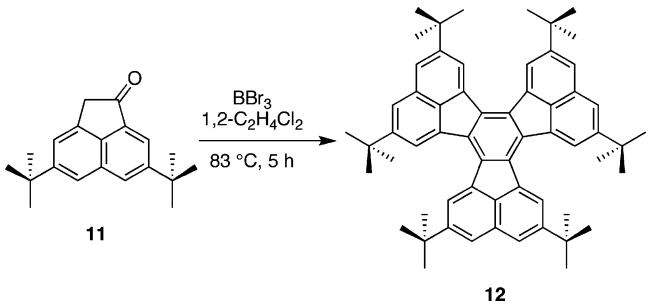

The first of these pathways, in which the enol of the dimer (**8**) functions as the nucleophile (eq 1), can be dismissed as improbable for electronic reasons. The γ-carbon atom of the dienol (**8**) will be relatively nucleophilic only if the diene

(6) Continued heating of this reaction mixture after the tetralone has been consumed leads only to the slow destruction of dimer **7** and no significant increase in the small amount of cyclic trimer **4** already formed: Amick, A. W.; Dombrowski, J. M.; Scott, L. T. Unpublished observation.

**SCHEME 3**




**SCHEME 4**




remains conjugated. Steric repulsions, however, will greatly diminish the population of the planar conformation required to achieve good orbital overlap. In such twisted systems, the α-carbon atom of a dienol generally exhibits greater nucleophilicity than the $\gamma$-carbon atom[7] (see the Supporting Information).

The pathway depicted in eq 2, on the other hand, looks quite reasonable. No serious steric impediments protrude above or below the plane of the protonated carbonyl group. Furthermore, the enhanced basicity of the ketone imparted by the additional α,$\beta$-unsaturation[8] ensures that the concentration of electrophile **9** will be high enough to compete for the enol of the monomer as the reaction proceeds.

With a $\beta,\gamma$-double bond, the dimer of α-tetralone (**7**) not only loses the kinetic advantage resulting from a high concentration of protonated dimer, but the protonated dimer is also a more crowded electrophile than the protonated monomer. Consequently, the second aldol step becomes slow, and dimer **7** builds up in concentration much faster than it proceeds on to the next step.

Little can be done to rectify this problem when it spoils a planned aldol cyclotrimerization reaction, unfortunately, but with the help of modern computational methods, the potential for encountering such a pitfall can at least be assessed in advance with some confidence.[1]

**Second Requirement: Dimer Must Stay in Solution.** Unlike α-tetralone (**3**), acenaphthenone (**5**) gives an α,$\beta$-unsaturated dimer (**10**), rather than a $\beta,\gamma$-unsaturated isomer. Nevertheless, the cyclotrimerization still fails under conditions that work well for indanone (**1**). In this case, it appears that the reaction fails because **10** precipitates out of the reaction mixture as soon as it is formed (Scheme 3).[5]

For the second aldol condensation (dimer + monomer → trimer) to compete successfully with the first one (monomer + monomer → dimer), the concentration of protonated dimer in solution must be high enough to compensate for the fact that it is a somewhat more hindered electrophile than the protonated monomer. Apparently, the protonated 18-carbon dimer of indanone (**9**) remains sufficiently soluble in hot acetic acid/HCl to complete the trimerization, whereas protonation does not render the 24-carbon acenaphthenone dimer (**10**) sufficiently soluble to be kinetically viable.

The dimer of acenaphthenone (**10**), being large and planar,[9] exhibits relatively poor solubility in most organic solvents. If the hypothesis is correct that this factor is playing a critical role in determining the outcome of the aldol cyclotrimerization, one would predict that the incorporation of solubilizing groups might salvage the reaction and prevent it from stalling at the dimer stage. To test our hypothesis, we decided to study the aldol cyclotrimerization of a soluble mechanistic probe molecule, 4,7-di-*tert*-butylacenaphthenone (**11**). A short synthesis of **11** has recently been reported by Amick et al.[10]

As anticipated, the addition of *tert*-butyl groups to acenaphthenone provides soluble intermediates that can be identified easily by $^1$H NMR spectroscopy (see the next section), and cyclic trimer **12** can be obtained in better than 50% isolated yield (Scheme 4).[10] This reaction yields no more than a trace of cyclic tetramer, a common byproduct of many aldol cyclotrimerizations.

We conclude that solubility of the aldol dimer is a second prerequisite for success in the aldol cyclotrimerization reaction.

**Temperature Requirements.** Many aldol cyclotrimerizations seem to work best only at relatively high temperatures, e.g., refluxing acetic acid (bp 117 °C) and even refluxing *o*-dichlorobenzene (bp 180 °C).[1] We wished to determine whether elevated temperatures are required to overcome high-energy barriers at one or more steps along the reaction pathway (Scheme 1) or if they simply serve to keep the aldol dimer dissolved. From the following studies on ketone **11**, *we conclude that there are no intrinsically high-energy barriers along the reaction pathway*; hexa-*tert*-butyldecacyclene (**12**) begins to appear in the cyclotrimerization of **11** even at 0 °C!

After screening several solvents and acids, we settled on boron tribromide in *o*-dichlorobenzene (ODCB) for the temperature studies described here. To the best of our knowledge, boron tribromide has not previously been used for the aldol cyclotrimerization reaction; however, we found that it gives cleaner reaction mixtures for NMR monitoring in the present case than $TiCl_4$ and the other Lewis acids examined. We will have more to say later about the choice of solvent.

The first aldol condensation between two molecules of **11** gives rise to two diastereomeric α,$\beta$-unsaturated dimers (*Z*- and *E*-**13**). Both are soluble in ordinary organic solvents, and both give characteristic singlets that are well separated from other peaks in the $^1$H NMR spectra taken of reaction mixtures prior to completion of the cyclotrimerization of **11** (see the Supporting Information). Dimer *Z*-**13** has been isolated in pure form as a high melting, bright-yellow solid.[10]

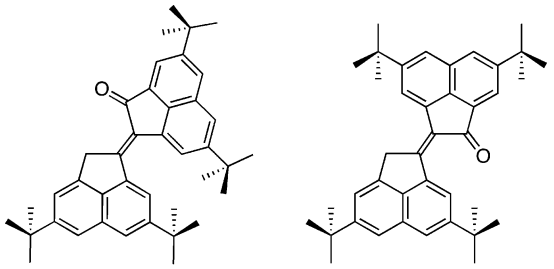
Aldol cyclotrimerizations of **11** catalyzed by $BBr_3$ in ODCB were run in triplicate, for 5 h each, at ten different temperatures from 0 to 180 °C. After quenching, each reaction mixture was

(7) See, for example: Noyori, R.; Inoue, H.; Kato, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3673−3678.

(8) See ref 1, p 28.

(9) No X-ray crystal structure of **10** is available, but DFT calculations at the B3LYP/6-31G* level of theory predict a planar geometry as the energy minimum. X-ray crystal structures of substituted derivatives of **10** are planar.[20]

(10) Amick, A. W.; Griswold, K. S.; Scott, L. T. *Can. J. Chem.* **2006**, *84*, 1268.



***E*-13** ***Z*-13**

worked up by a uniform protocol and analyzed by $^1$H NMR spectroscopy. The relative intensities of the characteristic signals for dimers *Z*-**13** and *E*-**13**, cyclic trimer **12**, and residual starting material **11** present at the end of each 5 h reaction are plotted in Figure 1A. No NMR signals could be detected for any of the reaction intermediates between the dimers (*Z*- and *E*-**13**) and the final cyclic trimer (**12**).

As Figure 1A shows, the aldol cyclotrimerization of **11** catalyzed by $BBr_3$ in *o*-dichlorobenzene reaches completion in 5 h at 55 °C. At higher temperatures, the amount of cyclic trimer (**12**) in this case actually decreases during the 5 h reaction time. In the $^1$H NMR spectra, new signals begin to appear that may result, in part, from the onset of acid-catalyzed "dealkylation" of **12**. This unwanted side reaction limits the use of **11** as a probe molecule for reactions run under forcing conditions.

At temperatures below 55 °C, the cyclotrimerizations proceed only part way in the 5 h before they are quenched. Signals for both dimers (*Z*- and *E*-**13**) can be seen, with the latter predominating at lower temperatures, but the concentration of dimers, taken together, always remains lower than that of starting material (**11**). Even at 0 °C, the first aldol step converts 32% of the starting material to dimers *Z*-**13** and *E*-**13** within the first 5 h, and a 1−2% yield of trimer already begins to appear. Clearly, none of the steps in this aldol cyclotrimerization require high temperatures.

Closer examination of the results in Figure 1A allows us to draw a second, tentative conclusion. The trends suggest that the *relative rates* of the first and second aldol steps may respond differently to temperature, at least in this test case. We note that when the reaction is run at low temperatures, the concentrations of the two dimers build up quite high, and only small amounts of trimer are formed during the first 5 h of the reaction. At progressively higher temperatures, the ratio of dimers to trimer at the end of 5 h is less skewed. In light of this trend, one would be wise, when optimizing the conditions for a new aldol cyclotrimerization, to examine the reaction not only at the lowest practical temperature but also at higher temperatures for shorter times.

**Solvent Requirements.** Figure 1B shows the results obtained by repeating the aldol cyclotrimerization of di-*tert*-butylacenaphthenone (**11**) with $BBr_3$ in 1,1,2,2-tetrachloroethane. This solvent has also been used in the past for aldol cyclotrimerizations,[1] in part because it boils at a relatively high temperature (bp 147 °C) and is stable to acid.

Qualitatively, the temperature profile in Figure 1B looks very similar to that in Figure 1A, but it is shifted. Not much happens at 0 °C; the buildup of dimers and the onset of trimerization is not seen until 25 °C, and the reaction is only 90% complete in 5 h at 55 °C. The composition of the reaction mixture after 5 h at 25 °C in 1,1,2,2-tetrachloroethane appears virtually identical with that of the reaction mixture in ODCB after 5 h at 0 °C

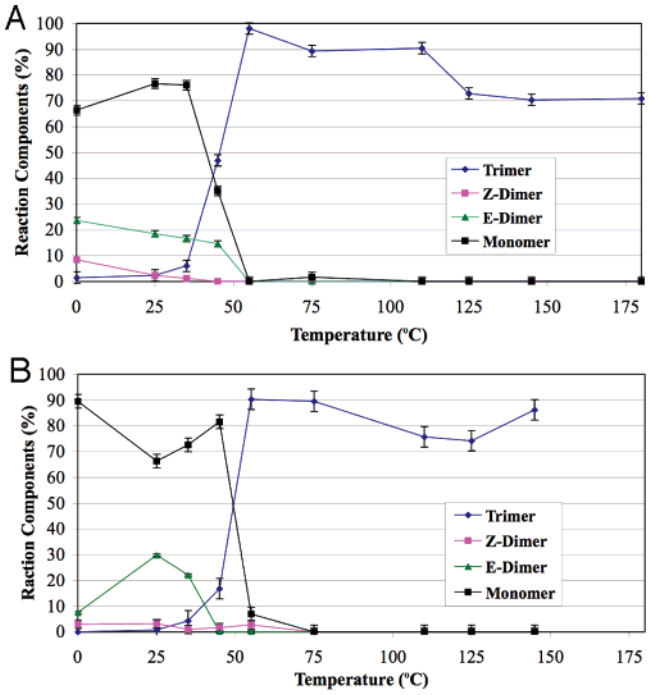



**FIGURE 1.** Compositions of the reaction mixtures ($^1$H NMR) after 5 h at different temperatures for the aldol cyclotrimerizations of **11** (50 mg each) with $BBr_3$ (11.2 equiv) in *o*-dichlorobenzene (A) and in 1,1,2,2-tetrachloroethane (B).

(compare parts A and B of Figure 1). From this comparison, then, *o*-dichlorobenzene seems to be a somewhat better choice as the solvent than 1,1,2,2-tetrachloroethane. The two have very similar dielectric constants (9.93 and 8.20, respectively)[11] and even more similar solvent $E_T(30)$ values (38.0 and 39.2, respectively);[12] however, the delocalized $\pi$-system of *o*-dichlorobenzene undoubtedly makes it more polarizable than 1,1,2,2-tetrachloroethane, and this may well contribute to its superiority. The difference in refractive index between these two solvents (1.552 and 1.494, respectively, at 20 °C)[13] can be taken as an indication of the difference in their polarizabilities.[14]

To probe the importance of solvent polarity, we searched for a solvent that matches one of these two with respect to polarizability but differs significantly in polarity. Toluene emerged as a reasonable choice: the refractive index of toluene is virtually identical with that of 1,1,2,2-tetrachloroethane (1.496 vs 1.494),[13] but toluene has a much lower dielectric constant (2.38 vs 8.20)[11] and solvent $E_T(30)$ value (33.9 vs 39.2)[12] than 1,1,2,2-tetrachloroethane.

A single point comparison between reactions run in toluene and 1,1,2,2-tetrachloroethane is revealing. At the end of 5 h at 55 °C, the reaction mixture from aldol cyclotrimerization of **11** with $BBr_3$ in 1,1,2,2-tetrachloroethane contains 90% trimer (**12**), 7% starting material, and 3% dimer *Z*-**13** (Figure 1B). By contrast, the corresponding mixture from the same reaction run

(11) Riddick, J. A.; Bunger, W. B. *Organic Solvents*: *Physical Properties and Methods of Purification*, 3rd ed.; Wiley-Interscience: New York, 1971.
(12) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 3rd ed.; Wiley-VCH: Weinheim, Germany, 2003.
(13) Refractive index values at 20 °C were taken from the following: *CRC Handbook of Chemistry and Physics*, 75th ed.; Lide, D. R., Ed.; CRC Press: Boca Raton, FL, 1994; Section 3.
(14) The polarizability of a liquid is directly proportional to its index of refraction: *CRC Handbook of Chemistry and Physics*, 75th ed.; Lide, D. R., Ed.; CRC Press: Boca Raton, FL, 1994; Section 10.

in toluene contains only 4% trimer (**12**), 96% dimer *Z*-**13**, and no remaining starting material. The dramatic reversal in the aldol product ratios clearly indicates that some degree of solvent polarity, in addition to polarizability, is advantageous for the cyclotrimerization. Toluene also proved to be less impervious to $BBr_3$ than 1,1,2,2-tetrachloroethane, giving rise to a number of solvent-derived hydrocarbon byproducts.

To probe next the importance of solvent polarizability, we searched for a solvent that has exceptionally high polarizability. Diiodomethane emerged as an interesting choice: the refractive index of diiodomethane at 20 °C (1.743)[13] is substantially higher than that of either ODCB or 1,1,2,2-tetrachloroethane (1.552 and 1.494, respectively). The dielectric constant (5.32)[11] and solvent $E_T(30)$ value (36.5)[12] for diiodomethane are both somewhat lower than those for ODCB and 1,1,2,2-tetrachloroethane, but its polarity is not as low as that of toluene. For the aldol cyclotrimerization of **11** with $BBr_3$ in diiodomethane, after 5 h at 55 °C, the reaction mixture contains 56% trimer (**12**), 40% starting material, and 4% dimer *Z*-**13**. Thus, the reaction proceeds more slowly than in ODCB and 1,1,2,2-tetrachloroethane, but the dimer continues rapidly on to trimer; its concentration does not build up. Polarizability, therefore, seems to be an important solvent attribute for this reaction.

Overall, in our experience, *o*-dichlorobenzene has the best combination of polarity and polarizability of any solvent we have found for the aldol cyclotrimerization. Furthermore, its high boiling point makes it convenient to use at temperatures well above 100 °C when such measures are required to prevent the dimers from precipitating out of solution.

**Brønsted Acids as Catalysts.** The preparation of truxene from indanone (**2** → **1**, Scheme 1) in 85% isolated yield stands out as one of the best aldol cyclotrimerizations ever reported.[3] The highest yield has been achieved by using a classical Brønsted acid system, concentrated HCl in hot acetic acid. Unfortunately, the inhospitable nature of aqueous acetic acid for larger ketones and their aldol dimers (e.g., acenaphthenone, **5**, see above) severely limits the generality of these conditions. Fortunately, *o*-dichlorobenzene and other chlorinated hydrocarbons dissolve a much wider range of organic compounds and have enough polarity and acid stability to serve as convenient media in which to run aldol cyclotrimerizations. $BBr_3$ and $TiCl_4$ both work as Lewis acid catalysts in these solvents, but the isolated yield of truxene from aldol cyclotrimerization of indanone in 1,2-dichloroethane is only 36% when $BBr_3$ is used as the catalyst, and the yield is even lower with $TiCl_4$.

The effectiveness of Brønsted acids in chlorinated hydrocarbon solvents in promoting aldol cyclotrimerizations has never been thoroughly explored. We decided to screen some Brønsted acids, using indanone (**2**), rather than di-*tert*-butylacenaphthenone (**11**), which suffers from acid-catalyzed dealkylation under forcing conditions. Our objective was to find conditions for converting indanone into truxene (**2** → **1**, Scheme 1) in good yield, using a high-boiling organic solvent that would be suitable for a wide variety of cyclic ketones. The 85% yield of truxene from indanone in acetic acid/HCl was the benchmark that we strove to replicate.

Adding 3.5 equiv of triflic acid ($CF_3SO_3H$) to a solution of indanone in 1,1,2,2,-tetrachloroethane produces an immediate color change to red. Heating the reaction mixture overnight at 105 °C fails to yield any truxene (**1**); only starting material (**2**) is recovered. Apparently, triflic acid simply protonates all of the ketone, essentially irreversibly, and the concentration of neutral enol never rises high enough for the aldol condensation to occur. This is entirely reasonable, since the p$K_a$ of protonated indanone (−3.65)[15] is much higher than that of triflic acid (ca −14).[16]

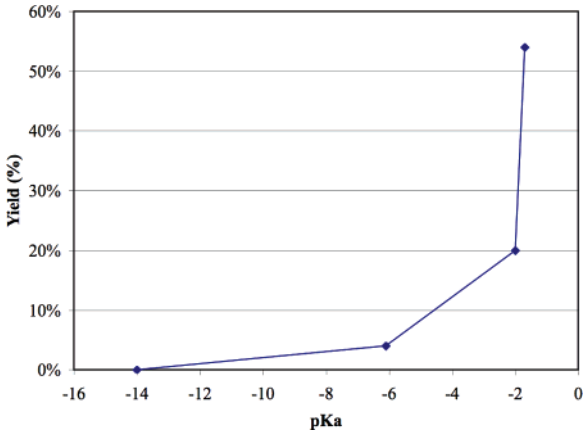



**FIGURE 2.** Yield of the cyclotrimerization of indanone (**2**) versus p$K_a$ of the acid catalyst used. Each reaction was run with 1.0 mmol of **2** and 3.5 equiv of acid in 1,1,2,2-tetrachloroethane at 105 °C for 16 h.

When the above experiment was repeated, using 3.5 equiv of triflic acid but with 3.5 equiv of acetic acid also added, truxene was formed in 4% yield. Under these conditions, protonated acetic acid (p$K_a$ = −6.1)[17,18] serves as the Brønsted acid catalyst. Using 3.5 equiv of methanesulfonic acid as the catalyst (p$K_a$ = −2.0)[18] raises the yield of truxene to 20%, but moving slightly further up the p$K_a$ scale to *p*-toluenesulfonic acid monohydrate (i.e., hydronium tosylate, p$K_a$ = −1.7)[16a] gives truxene in 54% yield (Figure 2).

These results indicate that the Brønsted acid catalyzed aldol cyclotrimerization of indanone in 1,1,2,2-tetrachloroethane works best when the p$K_a$ of the acid catalyst is at least 2 p$K_a$ units higher than that of the protonated ketone. Empirically, this suggests that high levels of protonated ketone (more than a few percent) are detrimental to the aldol cyclotrimerization. One possible explanation for this correlation is that high levels of protonated ketone could promote polymerization by interception of the trienol (see Scheme 1) before it can cyclize. High molecular weight materials invariably constitute a portion of the product mixture in these reactions.

Focusing on the *p*-toluenesulfonic acid monohydrate conditions, we examined the effects of various additives and discovered that the combined use of *p*-toluenesulfonic acid monohydrate and acetic acid (3.5 equiv of each) in 1,1,2,2-tetrachloroethane at 105 °C raises the yield for conversion of indanone to truxene from 54% to 64%. We speculate that the added acetic acid may play a role in solvation of the tosylate

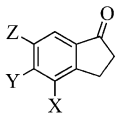
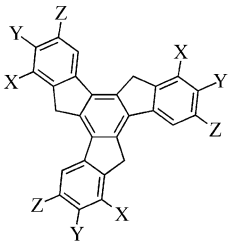
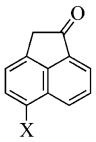
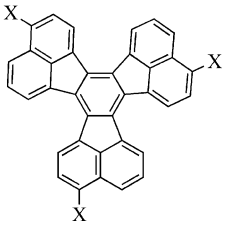
(15) Noto, R.; D'Anna, F.; Gruttadauria, M.; Lo Meo, P.; Spinelli, D. *J. Chem. Soc., Perkin 2* **2001**, 2043−2046.

(16) (a) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456−63. See also: (b) Engelbrecht, A.; Rode, B. M. *Monatsh. Chem.* **1972**, *103*, 1315−19. (c) Rode, B. M.; Engelbrecht, A.; Schantl, J. *Z. Phys. Chem.* **1973**, *253*, 17−24. (d) Benoit, R. L.; Buisson, C. *Electrochim. Acta* **1973**, *18*, 105−10. (e) Fujinaga, T.; Sakamoto, I. *J. Electroanal. Chem. Interfacial Electrochem.* **1977**, *85*, 185−201. (f) Guthrie, J. P. *Can. J. Chem.* **1978**, *56*, 2342−54.

(17) Arnett, E. M. In *Progress in Physical Organic Chemistry*; Cohen, S. G., Streitwieser, A., Jr., Taft, R. W., Eds.; Interscience: New York, 1963; Vol. 1, p 253.

(18) *Ionization Constants of Organic Acids in Solution* Serjeant, E. P., Dempsey, B., Eds.; IUPAC Chemical Data Series No. 23; Pergamon: Oxford, UK, 1979.

**TABLE 1. Aldol Cyclotrimerization Reactions Run with 3.5 equiv Each of *p*-TsOH·$H_2O$ and Propionic Acid as the Catalyst System in *o*-Dichlorobenzene at 105 °C for 16 h**

| Entry | Ketone | Product | Yield |
|---|---|---|---|
| Indanones | | | |
| 1. X = H (**2**), Y = H, Z = H |  |  | 67% (**1**) |
| 2. X = H (**14**), Y = Br, Z = H | | | 64% (**15**) |
| 3. X = $CH_3$ (**16**), Y = H, Z = H | | | 89% (**17**) |
| 4. X = H (**18**), Y = H, Z = $CH_3$ | | | 59% (**19**) |
| Acenaphthenones | | | |
| 5. X = H (**5**) |  |  | 66% (**6**) |
| 6. X = Cl (**20**) | | | 34% (**21**) |

anion, although how this improves the yield remains unclear. In anticipation that cyclotrimerizations of other ketones might require temperatures well above the boiling point of acetic acid (117 °C), we investigated also the influence of added propionic acid (bp 141 °C) and found that it works just as well as acetic acid, or even slightly better (67% yield).

In light of these results, we set out to see how broadly applicable the combined use of *p*-toluenesulfonic acid monohydrate and propionic acid (1:1) might be as a catalyst system for other aldol cyclotrimerizations in ODCB.

**Applications of the TsOH·$H_2O$/$CH_3CH_2COOH$/ODCB Catalyst System.** A particularly problematical case in our experience has been the aldol cyclotrimerization of unsubstituted acenaphthenone (**5**) to decacyclene (**6**). As reported in the introduction, heating acenaphthenone in acetic acid/concentrated HCl produces decacyclene in less than 5% yield. Using *p*-toluenesulfonic acid monohydrate and propionic acid (3.5 equiv of each) in *o*-dichlorobenzene at 105 °C for 16 h, however, converts acenaphthenone to decacyclene in 66% isolated yield. This is by far the best yield we have ever been able to achieve for the cyclotrimerization of acenaphthenone. Our previous best was 29%, using $SiCl_4$ in THF.[19]

Table 1 summarizes the results obtained by using the *p*-toluenesulfonic acid monohydrate/propionic acid catalyst system with indanone, acenaphthenone, and several derivatives of these aromatic ketones. In all cases but one, the cyclic trimers could be isolated in 59−89% yield, without any individual optimization of the reaction conditions.

Previous attempts to effect the cyclotrimerization of 5-chloroacenaphthenone (**20**) with $TiCl_4$ in *o*-dichlorobenzene have always given poor yields of complex product mixtures that contain not only the trimer but also the cyclic tetramer.[20] With the TsOH/propionic acid system, trimer **21** was obtained in a usable 34% yield, uncontaminated by cyclic tetramer.

## Conclusions

From the results of the limited screening summarized in Table 1, it is already clear that progress has been made toward the delineation of a widely applicable recipe for conducting aldol cyclotrimerizations of aromatic ketones. The use of *p*-toluenesulfonic acid monohydrate and propionic acid (3.5 equiv of each) in *o*-dichlorobenzene at 100 °C is recommended as a good starting point for new systems. The reaction is generally complete in less than 16 h and should be monitored to produce the optimum yield. If all of the starting ketone is consumed before the dimer is converted to cyclic trimer, it may be beneficial to repeat the reaction at a higher temperature.

There is still much to learn about the aldol cyclotrimerization reaction, but some key factors have been clarified. Dehydration of the initial aldol dimer to a $\beta,\gamma$-unsaturated ketone (e.g., **7**) will generally eliminate any chances of producing the cyclic trimer. Fortunately, DFT calculations can be used to determine in advance, with some confidence, whether the most stable enone will be $\beta,\gamma$-unsaturated (undesirable) or $\alpha,\beta$-unsaturated (required for a successful aldol cyclotrimerization).

Precipitation of the dimer from the reaction medium will likewise diminish the yield of cyclic trimer, sometimes to 0%. Several strategies can be invoked, either individually or in combination, to combat this problem: (1) incorporate solubilizing groups on the ketone, (2) run the reaction at a higher temperature, (3) switch to a better solvent. Polarizability and some degree of polarity both seem to be important prerequisites for a good solvent in these reactions; *o*-dichlorobenzene (ODCB) has about the best balance between these two qualities of any solvent we have examined.

High temperatures are not absolutely necessary for the aldol cyclotrimerization, but they can be advantageous when the intermediate dimers exhibit poor solubility. High temperatures also appear to suppress the build up of the aldol dimers. Lewis acids can function as catalysts in aprotic media but are often inferior to *p*-toluenesulfonic acid monohydrate.

We hope these observations will prove useful to others who wish to harness the power of the aldol cyclotrimerization reaction for the one-pot synthesis of triply annulated benzene rings.

## Experimental Section

**General Procedure for Aldol Cyclotrimerizations with Use of *p*-Toluenesulfonic Acid Monohydrate and Propionic Acid.** A 25 mL round-bottom flask was charged with the ketone (0.810 mmol), *p*-toluenesulfonic acid monohydrate (0.538 g, 2.83 mmol), propionic acid (0.21 mL, 2.8 mmol), and 0.69 mL of *o*-dichlorobenzene. The reaction mixture was heated to 105 °C for 16 h. After 16 h the crude reaction mixture was poured into methanol, which was slowly neutralized with 5 M NaOH. The precipitate was collected by filtration and washed with methanol and then ethanol to leave behind the desired cyclic trimer.

**Truxene (1).** From indanone (**2**) (1.36 g, 1.03 mmol), the general procedure described above gave 0.758 g (67%) of **1** as a pale yellow solid: mp >300 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.97 (d, $J$ =

(19) McComas, C. C. B.S. thesis, Boston College, Chestnut Hill, 1996.

(20) Ansems, R. B. M. Ph.D. Dissertation, Boston College, Chestnut Hill, 2004.

7.2 Hz, 3 H), 7.70 (d, $J = 7.6$ Hz, 3 H), 7.51 (t, $J = 7.6$ Hz, 3 H), 7.40 (t, $J = 7.6$ Hz, 3 H), 4.29 (s, 6 H).[3a,21]

**2,7,12-Tribromotruxene (15).** From 5-bromo-1-indanone (**14**) (0.171 g, 0.810 mmol), the general procedure described above gave 0.100 g (64%) of **15** as a pale yellow solid: mp >300 °C; $^1$H NMR (300 MHz, [$D_2$]1,1,2,2-tetrachloroethane, 100 °C) $\delta$ 7.86 (s, 3H), 7.80 (d, $J = 7.8$ Hz, 3H), 7.66 (d, $J = 8.1$ Hz, 3H), 4.27 (s, 6H); HRMS ESI (*m/z*) $[M]^+$ calcd for $C_{27}H_{15}Br_3$ ($M^+$) 575.8724, found 575.8735. Anal. Calcd for $C_{27}H_{15}Br_3$: C, 56.00; H, 2.61. Found: C, 55.90; H, 2.34.

**1,6,11-Trimethyltruxene (17).** From 4-methyl-1-indanone (**16**) (0.118 g, 0.810 mmol), the general procedure described above gave 0.92 g (89%) of **17** as a pale yellow solid: mp >300 °C; $^1$H NMR (400 MHz, [$D_2$]1,1,2,2-tetrachloroethane, 100 °C) $\delta$ 7.90 (d, $J =$ 8.0 Hz, 3H), 7.50 (t, $J = 8.0$ Hz, 3H), 7.28 (d, $J = 8.0$ Hz, 3H), 4.18 (s, 6H), 2.59 (s, 9H); $^{13}$C NMR (125 MHz, [$D_2$]1,1,2,2-tetrachloroethane, 83 °C) $\delta$ 142.6, 141.5, 137. 6, 135.2, 127.6, 127.4, 119.6, 35.5, 19.0; HRMS ESI (*m/z*) $[M]^+$ calcd for $C_{30}H_{24}$ ($M^+$) 384.1878, found 384.1876.

**3,8,13-Trimethyltruxene (19).** From 6-methyl-1-indanone (**18**) (0.118 g, 0.810 mmol), the general procedure described above gave 0.061 g (59%) of **19** as a pale yellow solid: mp >300 °C; $^1$H NMR (300 MHz, [$D_2$]1,1,2,2-tetrachloroethane, 100 °C) $\delta$ 7.78 (s, 3H), 7.64 (d, $J = 7.2$ Hz, 3H), 7.26 (d, $J = 7.2$ Hz, 3H), 4.27 (s, 6H), 2.57 (s, 9H); HRMS ESI (*m/z*) $[M]^+$ calcd for $C_{30}H_{24}$ ($M^+$) 384.1878, found 384.1875. Anal. Calcd for $C_{30}H_{24}$: C, 93.71; H, 6.29. Found: C, 93.46; H, 6.01.

**Decacyclene (6).** From acenaphthenone (**5**) (0.136 g, 0.810 mmol), the general procedure described above gave 0.080 g (66%) of **6** as a brown solid: mp >300 °C; $^1$H NMR (300 MHz, [$D_2$]1,1,2,2-tetrachloroethane) $\delta$ 8.65 (d, $J = 7.2$, 6H), 7.93 (d, $J = 7.8$ Hz, 6H), 7.75 (t, $J = 7.2$ Hz, 6H).[21]

**4,10,16-Trichlorodecacyclene (21).** From 5-chloroacenaphthenone (**20**)[20] (0.164 g, 0.810 mmol), the general procedure described above gave 0.051 g (34%) of **21** as a light brown solid: mp >300 °C; $^1$H NMR[22](400 MHz, $CDCl_3$) $\delta$ 8.59 (d, $J = 7.6$ Hz, 1H), 8.58 (dd, $J = 8.0$ Hz, $J = 2.0$ Hz, 1H), 7.96 (d, $J = 8.0$ Hz, 1H), 7.91 (d, $J = 7.6$ Hz, 1H), 7.91 (d, $J = 8.4$ Hz, 1H), 7.78 (d, $J = 7.6$ Hz, 1H), 7.57−7.54 (m, 1H), 7.51 (d, $J = 7.2$ Hz, 1H), 6.99 (dd, $J = 8.4$ Hz, $J = 7.2$ Hz, 1H), 5.05 (d, $J = 7.2$ Hz, 1H); $^{13}$C NMR[22] (125 MHz, $CDCl_3$) $\delta$ 163.0, 136.0, 135.4, 135.3, 135.1, 135.0, 134.3, 133.3, 133.0, 132.1, 131.9, 131.5, 130.3, 129.4, 128.7, 128.5, 127.7, 127.3, 126.4, 124.8, 124.3, 122.99, 53.6; HRMS ESI (*m/z*) $[M]^+$ calcd for $C_{36}H_{15}Cl_3$ ($M^+$) 552.0239, found 552.0248.

**Acknowledgment.** Financial support from the National Science Foundation is gratefully acknowledged. We thank Dr. Kenneth R. Metz for technical assistance, Dr. Ronald B. M. Ansems for a sample of 5-chloroacenaphthenone (**20**), and Restek Corp. for generously supplying GC columns.

**Supporting Information Available:** NMR spectra for new cyclic trimers **15**, **17**, **19** and **21**; experimental details for the attempted aldol cyclotrimerization of acenaphthenone (**5**) in concentrated HCl/HOAc (Scheme 3); representative NMR spectra, integration data, and experimental details for the solvent/temperature studies summarized in Figure 1; DFT calculations on dienol **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070080Q

(21) Drake, J. A. G.; Jones, D. W. *Org. Magn. Reson.* **1980**, *14*, 272.

(22) Two sets of peaks are seen in the $^1$H and $^{13}$C NMR spectra of decacyclene derivative **21**. Strong aggregation/face-to-face dimerization is expected in solution for large polycyclic compounds such as this,[23] and from the symmetry of the monomer, one would expect a *meso*-dimer and a *d,l*-dimer to be formed with nearly equal probability.

(23) De Frutos, O.; Granier, T.; Gomez-Lor, B.; Jimenez-Barbero, J.; Monge, A.; Gutierrez-Puebla, E.; Echavarren, A. M. *Chem. Eur. J.* **2002**, *8*, 2879.